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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,317	LEENDERS ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/15/09 has been entered.

This Office Action is in response to the Applicant's request for continued examination received 1/15/09. Claims 1-11 are pending. Claims 8 and 9 are withdrawn. No claims are cancelled. No claims have been amended. Claim 11 is new. Claims 1-7 and 10, 11 are examined in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim contains the negative limitation that "said anthracyclines do not include an antibody conjugate".

Negative limitations such as the proviso of claim 11 must still have support in the specification. M.P.E.P. § 2173.05(i) state:

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims...The mere absence of a positive recitation is not basis for an exclusion. Any claim

> containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support."

Indeed the Applicant does not have a disclosure of all anthracyclines that are not conjugated. While the Applicant does have specific Examples of anthracyclines in their disclosure such as doxorubicin, daunomycin, actinomycin D, and mitoxantrone, they do not limit that these anthracyclines are not conjugated because of the open language of "anthracyclines comprise". Indeed if the claim language were to limit the claim language of "consisting of" a particular anthracycline such as "consisting of doxorubicin" would remove this rejection since a specific anthracycline with a specific structure would be outside the scope of "*anthracycline**s***", which includes anthracycline derivatives.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) or 102(a) (b) (c) rejection of claims 1-5, 7 and 10 over Leskovar et al. (WO 89/09620 which has an English language equivalent document US 2002/0094542) were considered but not found persuasive.

The Applicant continues to argue that the term "anthracyclines" excludes anthracyclines that are conjugated to an antibody. The Applicant argues that the specification "gives no indications, neither explicitly nor implicitly, that anthracyclines include anthracyclines that are conjugated to an antibody" (Applicant's Response, pg 4 bottom). The Applicant continues to provide definitions and examples of the common

use, plain English definitions of Anthracyclines and that the broad use of the terms includes those compounds derived from *Streptomyces* bacteria and excludes anthracyclines with antibody conjugates since they "cannot come from or derive from *Streptomyces* bacteria".

However this is not convincing. M.P.E.P. § 2111 clearly directs the Examiner to use the "broadest reasonable interpretation consistent with the specification". M.P.E.P. § 2111.01 II clearly instructs the Examiner that "it is improper to import claim limitations from the specification" (see also M.P.E.P. § 2145). Indeed given that Lescovar et al. teach antibody conjugates of specific anthracyclines such as daunomycin, and doxorubicin (a.k.a. andriamycin) that would be considered by one of ordinary skill in the art as derivatives of anthracycline isolated since they maintain the fundamental polycyclic functionality common to anthracyclines but are simply *derivatized* with an antibiotic group. Therefore they would fall under the term of "*Anthracycline*s". The art is replete with references where anthracycline conjugated to antibodies continue to be considered "Anthracyclines" as supported by Angelucci et al. (U.S. Patent # 5776458, see Abstract and Structures 3-3").

The Applicant argues that Leskovar et al. teaches away from the claimed composition. However this is not convincing since it was detailed above that the invention as claimed includes the anthracycline-antibody conjugates of Leskovar et al.

The Applicant invokes M.P.E.P. § 2144.08 stating that the Genus disclosed by Leskovar et al. is too large to be considered prima facia obvious considering that "biotechnology is generally considered an unpredictable art"

(Applicant's Response, pg 6, last full paragraph). This argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The Applicant continues to argue that Leskovar et al. is using a completely different mechanism to treat a tumor with their composition. However compositions are defined by the structure of their components and if the composition is physically the similar or indeed the same, obviously it must have the same properties including mechanism (M.P.E.P. § 2112.01). The Applicant can rebut this assertion with evidence showing that the prior art products "do not necessarily possess the characteristics of the claimed product" (M.P.E.P. § 2112.01 I).

Applicants rely on the arguments used in traversing Leskovar et al. above rejection to also traverse Leskovar et al. in view of Houseman et al. without additional arguments. However, as explained above, the previous rejection stands. Therefore, the response set forth above to arguments also applies to Leskovar et al. in view of Houseman et al. and the rejections are repeated below with amendments to address new claim 11.

Claims 1-5, 7, 10 and new claim 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403) in light of support by Sugiura et al. (Gann, 1982). This reference is written in German. However it has a U.S. Patent Publication (US 2002/0094542) which is a 371 and as such is an English language equivalent document (see M.P.E.P., Appendix L, 35 U.S.C. 371 National stage: Commencement.) The Examiner will cite the U.S. Patent Publication for convenience, but the rejection remains over WO 89/09620.

These claims are to a combined pharmaceutical preparation comprising as active substances: (a) at least one compound having glutaminase activity (**GA**) and (b) at least one antineoplastic agent selected from platinum complexes and anthracyclines. Claim 2 limits claim 1 by teaching the compound having GA is glutaminase, glutaminase-asparaginase, glutaminase analog, derivative or modification of the same and is either of natural origin or is produced synthetically. Claim 3 limits that the compound with GA is from Pseudomonas. Claim 4 limit that the GA compound is modified. Claim 5 limits the type of anthracycline. Claim 7 teach the pharmaceutical preparation further comprises a pharmaceutically acceptable carrier for oral or parenteral administration.

Leskovar et al. teach a pharmaceutical preparation that comprises the Component A which includes anthracyclines such as doxorubicin and daunomycin that have been modified by conjugating them with antibodies (paragraphs 21-23). Leskovar et al. also teach that their pharmaceutical preparation can comprise antibody immunoconjugates of the enzymes asparaginase and glutaminase (paragraph 192).

Leskovar et al. does not specifically teach the addition of both the anthracyclines and glutaminase enzymes in the same composition. However Leskovar et al. does teach that antibody conjugates of xenogeneic proteins can be admixed with Component A and either administered parenterally or orally and modified with PEG (polyethylene glycol) (paragraph 25-26). One of ordinary skill in the art would recognize that that a composition with active substances such as enzymes and anthracyclines would need to be mixed with a pharmaceutically acceptable carrier such as water to be administered parenterally or orally.

It would therefore have been obvious for the person of ordinary skill in the art to modify the invention of Leskovar et al. to combine an enzyme such as glutaminase with component A, which they teach as an anthracycline such as doxorubicin. Leskovar et al. provides express motivation and reasonable expectation of success by stating that "conjugates, composed of xenogeneous proteins...can be admixed to the component A" (paragraph 26).

Furthermore it would be obvious to combine the anthracycline and glutaminase since they are two components known for the same purpose (see M.P.E.P. § 2144.06). In this case the treatment of cancer (paragraph 140 and 192). This would apply to anthracyclines that are immunoconjugated or not, since the art is replete with references that unmodified anthracyclines alone are effective against the treatment of cancer as supported by Sugiura et al. (See Table on pg 209).

While Leskovar et al. does teach the use of glutaminase and asparaginase (paragraph 192) they do not teach that the compound having glutaminase activity is

Pseudomonas 7A glutaminase-asparaginase. However it would be obvious to one skilled in the art that any glutaminase regardless of its source will perform the same chemical reaction and can therefore be used for the same purpose unless evidence to the contrary is provided (M.P.E.P. § 2144.06).

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the reference listed above and as such claims 1-5, 7 and claim 10 are not allowable.

Claim 1-7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403) as applied to claim 1-5, 7 and new claim 10 above, and further in view of Housman et al. (U.S. Patent # 6,200,754, 2001).

The details of clams 1-5, 7 and 10 and their rejection are described in the above 103(a) rejection over Leskovar et al.

Claim 6 limits the pharmaceutical preparation comprising cis-platinum, oxaliplatinim or/and carboplatinum.

While Leskovar et al. teach the use of other DNA crosslinking compounds such as mitomycin C (Leskovar et al. paragraph 23) in a composition for cancer treatment he does not teach the specific use of DNA crosslinking agent cis-platinum. However Housman et al. teach that mitomycin C and cis-platinum are both DNA crosslinking agents (col 22, lines 14-15) and one of ordinary skill in the art would recognize them as common drugs for cancer treatment (col 21, line 55 to col 22, line 20). Therefore it

would be obvious to replace cis-platinum or other DNA crosslinking agents such as oxaliplatinum and carboplatinum since these are art-recognized equivalents for the same purpose (M.P.E.P. § 2144.06).

New Rejections Necessitated by Amendment

This new rejection is made in response to new claim 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugiura et al. (Gann, 1982).

Sugiura et al. teach a pharmaceutical preparations for in a pharmaceutical acceptable carrier (pg 208 and 209, Table II) that are administered parenterally to rats with tumors (Materials and Methods, pg 206 and 207). These compositions include anthracyclines such as Mitomycin C, adriamycin (a.k.a. doxorubicin), actinomycin D and daunomycin in carriers such as saline (Table on pg 209). Leskovar et al. also teach that their pharmaceutical preparations such as cis-platinum (a.k.a. cis-dichlorodiammine Pt(II), pg 208) and enzymes such as glutaminase-asparaginase (page 210) in saline.

Sugiura et al. does not specifically teach the addition of both the anthracyclines and glutaminase enzymes in the same composition. M.P.E.P. § 2144.06 states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Therefore it is *prima facie* obvious to one of ordinary skill in the art to add more the Anthracyclines or the *cis*-platinum compositions together into one composition of since they are all known for the same purpose.

While Sugiura et al. does teach the use of glutaminase-asparaginase (pg 210) they do not teach the source is specifically *Pseudomonas* 7A glutaminase-asparaginase. However it would be obvious to one skilled in the art that any glutaminase-asparaginase regardless of its source will perform the same chemical reaction and can therefore be used for the same purpose unless evidence to the contrary is provided (M.P.E.P. § 2144.06).

Therefore claims 1-3, 5-7, 10 and 11 are obvious in view of the above reference.

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugiura et al. as applied to claims 1-3, 5-7, 10 and 11 above, and further in view of Roberts et al. (J. Gen. Virology, 1991).

While Sugiura et al. teach the use of the enzyme **glutaminase-asparaginase** (**PGA**) to treat tumors they do not teach that PGA is modified with **polyethylene glycol** (**PEG**). Regardless this would be obvious to one of ordinary skill in the art by the time the invention was made in view of the teachings of Roberts et al. who teach that PGA half-life is increased after PEG modification (pg 304, col 1, last paragraph). It would be obvious to one of ordinary skill in the art to use the PEG modified PGA of Roberts in the composition of Sugiura et al. since this is the simple substitution of an improved version of the same enzyme that still performs the same reaction, thus having the same purpose, but has a longer half-life (M.P.E.P. § 2144.06 II and (KSR International v. Teleflex Inc. 550 U.S. ___, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007)).

Therefore claims 1-7, 10 and 11 are obvious in view of the above references.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Leon B Lankford/
Primary Examiner, Art Unit 1651